UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Note to Reader
September 9, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply, EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, if unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues

available in the information in this docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack Housenger, Acting Director
Special Review and Reregistration
Division

HED DOC NO. 012557

DATE: **March 26, 1998**

MEMORANDUM

SUBJECT: ***FENTHION:*** - **RE-EVALUATION** -Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland
Executive Secretary,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Stephen Dapson, Branch Senior Scientist
Toxicology Branch 2
Health Effects Division (7509C)

PC Code: 053301

On March 19, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) convened to discuss fenthion and evaluated the newly submitted acute (§81-8) and a subchronic (§82-7) neurotoxicity studies, reviewed the neurotoxicity data from the published literature and determined the need for a developmental neurotoxicity study. The HIARC also re-evaluated the previous (10/18/97) conclusions and made recommendations to the FQPA Safety Committee with regard to the application of the FQPA safety factor. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were William Burnam, Robert Fricke, Mike Metzger, Melba Morrow, John Redden, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Members in absentia were Karl Baetcke and Karen Hamernik. Data was presented by John Doherty of Toxicology Branch 2.

Data Presentation: _____

John Doherty
Toxicologist

Report Preparation: _____

Jess Rowland.
Executive Secretary

I. INTRODUCTION

On October 5, 1995, the Health Effects Division's RfD/Peer Review Committee recommended that an RfD for fenthion be established based upon a comprehensive assessment of plasma ChE and RBC and/or brain AChE inhibition in humans, monkeys, rats, dogs and mice. The data from all these studies indicate that: 1) inter-species variability and/or susceptibility of ChE or AChE to fenthion is not a major factor; 2) plasma ChE is usually more susceptible than RBC or brain AChE to fenthion inhibition but the differences are not always large and differed in the species tested; 3) differences in the susceptibility of males and females were also variable among the different species, females, however, were more susceptible in monkeys but females were not tested in humans.

For practical purposes, the Committee used the threshold NOEL/LOEL of 0.02 mg/kg/day for plasma ChE inhibition to set the RfD for this chemical. It should be noted that 0.02 mg/kg/day was also considered to be a threshold NOEL/LOEL in the human study. However, because of the human study shortcomings such as the limited number of subjects in conjunction with the lack of data on females, the Committee felt that the primate study would be more reliable for this purpose.

An uncertainty factor (UF) of 10 was applied to account for intra-species variability. The Committee felt that no uncertainty factor for inter-species extrapolation would be required since inter-species variability was not evident in this case. However, an additional UF of 3 was applied to account for the lack of a definite NOEL for the monkey and human studies, the lack of data on females in the human study, and the fact that brain AChE was inhibited at dose levels comparable to those causing plasma cholinesterase inhibition in some species.

On this basis the Committee established a Reference Dose (RfD) of 0.0007 mg/kg/day based on a threshold NOEL/LOEL of 0.02 mg/kg/day and an Uncertainty Factor of 30 which included a 10 x for intra-species variation and an additional 3 x to account for the lack of a definite NOEL (*Memorandum:* G. Ghali, HED to G. LaRocca, RD, dated 3/16/97).

On December 19, 1995, the Health Effects Division's Toxicology Endpoint Selection (TES) Committee selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments (TES Document dated 1/26/96).

On September 2, 1997 the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) addressed the potential enhanced sensitivity of infants and children from exposure to fenthion as required by the Food Quality Protection Act (FQPA) of 1996. At this meeting the HIARC determined that the additional 10 x factor as required by FQPA should be retained because of the lack of acute and subchronic neurotoxicity studies (i.e., data gaps) as well as evidence of neurotoxicity (both *in vivo* and *in vitro)* in studies published in the open literature (*Memorandum:* J. Rowland to K. Whitby, dated 10/18/97).

On March 19, 1998, the HIARC evaluated acute (§81-8) and subchronic (§82-7) neurotoxicity studies that have been submitted since the HIARC meeting (in September) and their impact/relevance in risk assessments. In addition, the HIARC reviewed the data available in the published literature, determined the need for a developmental neurotoxicity study, re-evaluated the previous (10/18/97) conclusions, and made recommendations to the FQPA Safety Committee with regard to the application of the FQPA safety factor.

The reader is referred to the RfD, TESC and HIARC reports (cited above) for Executive Summaries of the studies as well as the rationale for doses and endpoints selected for the various exposure scenarios and the assessment of the FQPA requirement. Only the conclusions of the March 19 HIARC meeting are presented in this report.

II. EVALUATION OF THE NEUROTOXICITY STUDIES.

(I) Acute Neurotoxicity Study (MRID No. 44326401)

In an acute neurotoxicity study four groups of 18/sex Wistar strain rats were dosed with fenthion (94.6% purity) in corn oil (5 ml/kg) and assessed daily for clinical signs, FOB and motor activity at about 5 hours post dosing and on days 7 and 14. After sacrifice on day 14, the rats were perfused and assessed for neurohistopathology. The dose levels were 0, 1, 50 or 125 mg/kg for males and 0, 1, 75 or 225 mg/kg for females.

At 50 mg/kg for males and 75 mg/kg for females there were several parameters affected to indicate consequences of inhibition of ChE/AChE. The *principle* parameters affected included decreased motor activity, presence of muscle fasciculation (all males and 11/12 females), repetitive chewing (all males and females), gait impairment (all males and females), decreased body temperature (0.9 ^{o}C, $p < 0.05$ males), pupil constriction (9/12 males and all females), decreased body weight and gain. At 125 mg/kg in males the same symptoms increased and in addition there were convulsions and several other treatment-related reactions. At 225 mg/kg in females there were 4 deaths as well as increased incidence and severity of the symptoms. The decrease in motor activity reversed slowly with there being some symptoms remaining at day 14. See review for complete list of parameters affected. **For neurotoxicity, the NOEL was 1 mg/kg for both sexes and the LOEL was 50 mg/kg in males and 75 mg/kg in females based mainly on muscle fasciculation and related parameters.**

At 1 mg/kg plasma ChE (-23%, not significant), RBC AChE (- 22 %, $p < 0.05$) and brain AChE (-9%, $p < 0.01$) were inhibited in females. Males showed decreases but they did not reach statistical significance. At 50 mg/kg for males and 75 mg/kg for females and above inhibition was always greater than 76%. **The NOEL and LOEL for inhibition of ChE/ACHE is < 1 mg/kg (females more affected than males).**

(ii) Subchronic Neurotoxicity Study (MRID No. 44339401)

In a subchronic neurotoxicity study, fenthion technical (94.3% a.i.) was administered to Wistar rats (12/sex/dose) by feeding at dose levels of 0, 2, 25 or 125 ppm (0, 0.13, 1.63 or 8.50 mg/kg/day for males; 0, 0.17, 2.19 or 12.62 mg/kg/day for females) for 13 weeks. The rats were evaluated by functional observation battery (FOB) and motor activity testing at pretest and during weeks 4, 8, and 13 of treatment. Six rats/sex/group were evaluated for neuropathology and the remaining 6 rats/sex/group were evaluated for cholinesterase activities (plasma, erythrocyte, and brain) during weeks 4 and/or 14 of treatment.

At 25 ppm there was decreased body weight (5-7%, $p < 0.05$) and body weight gain (15-17%) in females, body weight (3-4%) and weight gain (4-10%) in males was also lower but statistical significance was not attained. At 125 ppm, body weight effects were more pronounced and clinical signs indicated palmospasms and related reactions , FOB assessment indicated muscle fasciculations (6/12 males and 8-9 females)and related cholinergic responses (gait abnormalities, slight tremors (one female) and stilted gait). Motor activity was also decreased. No pathological lesions in the nerve tissue including the eye and optic nerve or in the epididymis were noted. **For neurotoxicity, the LOEL was 25 ppm (1.63 mg/kg/day for males and 2.19 mg/kg/day for females) based mainly on body weight and muscle fasciculations. The NOEL was 2 ppm (0.13 mg/kg/day for males and 0.17 mg/kg/day for females).**

At 2 ppm, plasma ChE was inhibited 16-17% ($p <.05$) in males. Females were also 17-21% lower but statistical significance was not attained probably because of the poor precision of the data (i.e. large standard deviations). At 25 ppm, plasma ChE (~57%♂, 81%♀), RBC ACHE (56-65%♂, 78%♀) and brain AChE (47%♂, 58%♀) were definitely inhibited. **The NOEL and LOEL for plasma ChE inhibition is < 2 ppm (0.13 mg/kg/day for males and 0.17 mg/kg/day for females).**

II. EVALUATION OF OPEN LITERATURE DATA

In the process of preparing for development of the toxicity chapter for the RED for fenthion, Dr. William Boyes of EPA's Neurotoxicology Division in RTP was consulted and requested to send papers on his work and other related papers on fenthion. In a meeting with Karl Baetcke, Marion Copley and John Doherty it was determined that the dose levels used in these papers were in excess of those dose levels known to inhibit ChE/AChE and the methods used were experimental and not conventional methods already validated for regulatory purposes and often subcutaneous administration was used. Overall, it was determined that these papers were not relevant to the risk assessment purposes of fenthion.

In addition two publications were reviewed. In one paper [Tandon *et al.Toxicology* and *Applied Pharmacology* **125:** 271-280 (1994)], an acute dose of fenthion was assessed at 100 mg/kg administered subcutaneously and assessments on muscarinic receptors in the retina were investigated. The paper reported that apparently persistent effects (i.e., up to 56 days) on the retina including inhibition of AChE, inositol phosphate release and density of muscarinic receptors. The paper suggested that the effects on the retina may not be related solely to the potential for fenthion to inhibit ChE/AChE. This study is not considered appropriate for risk assessment but is useful in understanding the possible mechanisms of fenthion toxicity. Fenthion will be regulated at a dose level much below the 100 mg/kg assessed in this study based on its effects on ChE/AChE in other studies.

In the other paper [Moser, *Neurotoxicology and Teratology* **17**:617-625 (1995)] fenthion (dose levels of 0, 15, 75 or 150 mg/kg by gavage) was assessed in the Long-Evans strain rat. This same manuscript also assessed aldicarb, carbaryl, parathion, DFP, chlorpyrifos and diazinon in the FOB and motor activity protocols. The dose levels tested for fenthion were similar to the dose levels tested in the studies recently submitted by the registrant. Dr. Moser's paper, however, did not include assessment of inhibition of ChE/AChE. For comparison purposes, the studies submitted by the registrant established a NOEL and LOEL of 1 mg/kg (both sexes) and 50 mg/kg for males and 75 mg/kg for females for systemic effects based on muscle fasciculations and related effects. Dr. Moser did not actually indicate a NOEL and LOEL for systemic effects but described effects at the 150 mg/kg or the high dose only. Thus, the registrant's study is considered to better describe the acute responses to treatment of fenthion since it indicates toxicity at a lower dose.

As for the evidence of neurotoxicity in published studies, it was concluded that these studies generally used higher dose levels and nonconventional routes of administration (i.e., subcutaneous) and thus are not considered consequential for regulatory risk assessment purposes. The data bases generated by the conventional studies (submitted to the Agency) already establish NOELs and LOELs at lower doses based on a sensitive endpoint (i.e., cholinesterase inhibition).

III. FQPA CONSIDERATIONS

1. Adequacy of Data Base

The data base to assess the *in utero* and postnatal exposures of fenthion included prenatal developmental toxicity studies in rats and rabbits as well as a two-generation reproduction study in rats. In addition, adequate neurotoxicity studies, following single and repeated exposures are available to characterize the neurotoxic potential of fenthion.

2. Determination of Susceptibility

Prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility of rats or rabbit fetuses to *in utero* exposure to fenthion. There was no indication of increased susceptibility in the fetuses as compared to parental animals in the two generation reproduction study. In these studies, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

3. Developmental Neurotoxicity

The HIARC, based on a weight-of-the-evidence basis determined that a developmental neurotoxicity study is **not required**. This decision was based on the following factors: 1) no evidence of delayed type neuropathy, inhibition of neurotoxic esterase or neuropathology in the acute delayed neurotoxicity study in hens, 2) no treatment-related histopathological lesions of the nervous system in the acute neurotoxicity study in rats; 3) no treatment-related pathological lesion in the nerve tissues in the subchronic neurotoxicity study in rats; and 4) there was no evidence of developmental anomalies, including abnormalities in the development of fetal nervous system in the pre-and/or post natal studies. It is noted that this decision is a reversal of a previous decisions in which this study was identified as a Data Gap (HED Doc. No. 011804).

4. Determination of the FQPA Factor:

At the September 12, 1997 meeting the HIARC concluded that the additional 10 x factor should be retained due to the lack of critical neurotoxicity studies (acute and subchronic) which precluded the assessment of the neurotoxic potential as well as the evidence of neurotoxicity seen in published studies.

Since then the data gaps have been satisfied by the submission of the critical studies. Overall, these studies did not indicated toxicity or cholinesterase inhibition at dose levels lower than those previously selected and currently used for risk assessments and there were no treatment-related histopathological lesions seen in the nervous system. As for the evidence of neurotoxicity in published studies, these studies generally used higher dose levels and nonconventional routes of administration (i.e., subcutaneous) and thus are not considered consequential for regulatory risk assessment purposes. The data bases generated by the conventional studies (submitted to the Agency) already establish NOELs and LOELs at lower doses based on a sensitive endpoint (i.e., cholinesterase inhibition).

Based on hazard assessment, the HIARC, recommends that any additional 10 x factor related to hazard considerations should be removed because:

(i) The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to fenthion.

(ii) No evidence of developmental anomalies, including abnormalities in the development of fetal nervous system was observed in the pre-and/or post natal studies.

(iii) There are no data gaps for the critical studies.

However, the final recommendation on the application of the FQPA factor for the protection of infants and children from exposure to fenthion as required by FQPA, **will be made during risk characterization by the FQPA Safety Committee.**

VI. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE	ENDPOINT	STUDY
Acute Dietary	NOEL= 0.07 mg/kg	Plasma cholinesterase inhibition	Human Study
	UF =10	**Acute RfD = 0.007 mg/kg**	
Chronic Dietary	NOEL=0.02 mg/kg/day	Plasma cholinesterase inhibition .	Monkey/Human Study
	UF=30	**Chronic RfD = 0.0007 mg/kg/day**	
Short-Term (Dermal) [a]	Oral NOEL= 0.07 mg/kg/day	Plasma cholinesterase inhibition.	Human Study
Intermediate-Term (Dermal) [a]	Oral NOEL= 0.02 mg/kg/day	Plasma cholinesterase inhibition.	Human Study
Long-Term (Dermal) [a]	Oral NOEL= 0.02 mg/kg/day	Plasma cholinesterase inhibition.	Human study
Inhalation (Any Time Period) [b]	LOEL= 0.209 mg/L	Cholinergic signs and mortality.	Acute Inhalation - Rat

a = A dermal absorption factor of 20% should be used for dermal risk assessment since an oral NOEL was identified. The TESC recommended a MOE of 30 for dermal risk assessments.

b= An inhalation absorption factor of 100% (default) should be used. The acceptable MOE for inhalation risk assessments will be determined made after evaluation of the resulting MOE based on the LOEL provided.